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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,242	06/20/2003	Phillip Dan Cook	ISIS-5213	6684
32650	7590	05/17/2005	EXAMINER	
WOODCOCK WASHBURN LLP ONE LIBERTY PLACE - 46TH FLOOR PHILADELPHIA, PA 19103			EPPS FORD, JANET L	
			ART UNIT	PAPER NUMBER
			1635	
DATE MAILED: 05/17/2005				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/601,242

Applicant(s)

COOK ET AL

Examiner

Janet L. Epps-Ford, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44,47 and 49-68 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44,47 and 49-68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 20 June 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>7-28-03</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 44, 47, and 49-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

Claims 44, 47, and 49-58 are broadly drawn to the treatment of an organism having a disease characterized by the undesired production of protein comprising contacting the organism with a compound comprising a plurality of units linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid. The instant method broadly encompasses contacting an organism with a compound that is hybridizable to a complementary nucleic acid that is unrelated to the protein that is associated with the disease to be treated. The claim broadly reads on the treatment of an unspecified disease comprising contacting a compound of unspecified sequence that is hybridizable to an unspecified nucleic acid.

Claims 59-68 are broadly drawn to methods of concurrently enhancing hybridization and RNase H activation in an unspecified organism comprising the step of contacting the organism in an unspecified manner with an oligonucleotide of the invention having an unspecified sequence. The instant claims broadly encompass a method of treatment since the method is to be practiced *in vivo* in an organism.

The successful treatment of a disease by pharmaceutical composition comprising an antisense compound was unknown in the art at the time the application was filed. The quantity of experimentation required to practice the invention as claimed would require determining the structures of the mRNA targets *in vivo*, and the structures of the modified antisense oligonucleotides, modes of delivery in a *in vivo* such that the processing of said mRNA target is inhibited at a significant level and for a sufficient amount of time to produce the desired therapeutic effect. At the time of filing, neither the specification as filed, nor the prior art, provided any specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In regards to the amount of direction or guidance presented, the specification as filed does not provide sufficient guidance and/or instruction that would teach one of skill in the art how to successfully treat an organism having a disease associated with the undesired production of a protein in an organism comprising contacting said organism with a compound comprising a plurality of units linked by covalent linkages in a sequence that is hybridizable to a complementary nucleic acid. The specification as filed provides only guidance for practicing methods *in vitro* (see pages 41-46), wherein said methods comprise contacting cells *in vitro* with

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a compound that comprises a sequence that is hybridizable to a nucleic acid that is associated with the expression of human ras. The specification as filed provides only information regarding the ability of antisense treated cells to reduce the level of human ras in vitro by measuring the level of human ras mRNA in antisense treated cells in comparison to a control (see procedures 1-5). The examples do not provide any direct evidence of phenotypic effects on the antisense treated cells, for example there is no indication that cell growth was inhibited. Furthermore, the instant specification does not provided any clear nexus between inhibiting human ras by antisense administration in human cells or tissues wherein said antisense resulted in the treatment or prophylaxis of a disease or condition associated with ras in said human cells or tissues.

Regarding the level of predictability or unpredictability associated with the antisense therapeutic art at the effective filing date of the instant application, Crooke (1998), states “extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted].” Furthermore, Crooke describes a variety of factors that influences the activity of antisense-based compounds. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors: length of oligonucleotide, modifications, and sequence of oligonucleotide and cell type. The influence of non-antisense effects, for example phosphorothioate oligonucleotides tend to bind non-specifically to many proteins, wherein such protein binding influences cellular uptake, distribution, metabolism and excretion of said oligonucleotide. Additionally, non-specific

protein binding may produce effects that can be mistakenly interpreted as antisense activity, and may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may non-specifically interact with other biological molecules, such as lipids, or carbohydrates, wherein the chemical class of oligonucleotide will influence such interactions studied (Crooke, 1998; p. 3). Crooke clearly taught that as of the effective filing date of the instant application there was a significant level of factors, which influence the behavior of antisense based, compounds thereby rendering the activity of antisense compounds unpredictable.

Branch (1998) also taught that “Scientist seek to use the [antisense] molecules to ablate selected genes and thereby understand their functions and pharmaceutical developers are working to find nucleic acid based therapies. However, the antisense field has been turned on its head by the discovery of ‘non-antisense’ effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism.” In addition, Branch teaches that the successful delivery of antisense/ribozymes *in vivo* is unpredictable, the internal structures of the targeted RNA molecules and their association with cellular proteins can render target sites totally inaccessible *in vivo*. Moreover, Branch states that “[H]owever, their (*antisense molecules and ribozymes*) unpredictability confounds research applications of nucleic acid reagents.”

Jen et al. (*Stem Cells*, Vol. 18: 307-319, 2000) provide a review of the challenges that remain before antisense-based therapy becomes routine in therapeutic settings. According to Jen et al. many advances have been made in the antisense art, but also indicate that more progress needs to be made. Moreover Jen et al. conclude that “[G]iven the state of the art, it is perhaps

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not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive.” It is also concluded that “[A] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy.” (see page 315, last two paragraphs).

It is apparent from Branch, Crooke, and Jen et al. that the art of antisense base therapeutics (at the time of filing) is unpredictable and those highly skilled in the art are working towards making the antisense therapy more predictable have many obstacles to overcome. Therefore, claims to antisense based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the antisense art.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single gene is inhibited and the desired secondary effect (treating an organism with a disease associated with the undesired production of a protein) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 59-68 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,326,199 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims and the pending claims are limited to a method of concurrently enhancing hybridization and RNASE H in a cell. However, the issued claims differ from the pending claims to the extent that the issued claims are limited to a method in a cell, and the instant claims are drawn to a method that is practiced within the context of an organism. The instantly claimed methods are practiced within an organism, these claims overlap with the scope of the issued claims to the extent that the issued claims encompass wherein the claimed method is practiced in a cell within the context of an organism.

The scope of the instant claims is anticipated by the issued claims which encompass methods practiced within an isolated cell, a cell within the context of a population of cells (i.e. cell line, culture, etc.), and wherein the cell is within an organism.

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An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claim(s) 59-68 fall entirely within the scope of issued claim(s) 1-10 of US Patent No. 6,326,199.

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5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571)272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Janet L. Epps-Ford, Ph.D.
Patent Examiner
Art Unit 1635

JLE